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Please find below and/or attached an Office communication concerning this application or proceeding.

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Office Action Summary	Application No.	Applicant(s)	
	09/462,408	SCHMIDT ET AL.	
	Examiner	Art Unit	
	BJ Forman	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other: .

DETAILED ACTION

Specification

1. This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-26 are indefinite in being replete with relative, non-specific, redundant and undefined terms and phrases e.g. "sufficient for", "capable of", "reaction zone", "uniquely resolvable" and "relatable to". Some specific examples of the indefinite language are detailed below. The claims are drawn to method for characterizing DNA, but the claims are not set forth in positive and active method steps such that the subject matter of the claims is clear. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6. It is suggested that the claims be amended to recite positive and active method steps.

b. Claims 1-20 and 25-26 are indefinite in Claim 1 because the claim is drawn to a method for characterizing DNA, but the method does not recite steps for DNA characterization. It is suggested that Claim 1 be amended to recite method steps for DNA characterization.

c. Claims 2-17 are indefinite in Claim 2 because it is unclear at what step of Claim 1 the further method steps of Claim 2 are performed. It is suggested that Claim 2 be amended to clarify e.g. replace "which further" with wherein providing a population of DNA fragments".

d. Claims 3-25 are indefinite for the repeated recitation "mixture of nucleotides sufficient for hybridizing" because "sufficient" is a relative term which requires definition or criteria for determining. It is suggested that all the claims be amended to clarify e.g. delete "sufficient" or recite a definition or criteria for determining "sufficient".

e. Claims 3-25 are indefinite in the repeated recitation "modified nucleotide which is capable of polymerizing to the second strand of DNA" because it is unclear whether the recitation is a method step of polymerizing a nucleotide to the second strand. It is suggested that all the claims be amended to clarify e.g. replace "is capable of polymerizing" with "hybridizes".

f. Claims 6 and 7 are indefinite in the recitations "reaction zones" because the recitations lack proper antecedent basis in Claim 1. The claims are further indefinite because "reaction zones" are not defined in terms of the method and therefore it is unclear what limitations are being claimed. It is suggested that the claims be amended to provide antecedent basis and to define "reaction zone".

g. Claims 9-10 and 21-22 are indefinite in the recitation "removing unpolymerized nucleotides" because the recitation lacks proper antecedent basis in the claim which merely recites nucleotides "capable of polymerizing". It is suggested that the claim be amended to clarify e.g. as stated above, replace "capable of polymerizing" with "hybridizing" and replace "unpolymerized" with "unincorporated" or "unhybridized".

h. Claims 9-24 are indefinite in the recitation "all combinations of sequences being present in the array" because it is unclear which "sequences" and which "combinations" are being claimed. It is suggested that the claims be amended to clarify.

i. Claims 11 and 12 are each indefinite in the repeated recitation "modified nucleotide which is capable of ligating to the second strand of DNA" because it is unclear whether the recitation is a method step of ligating or a characteristic of the "modified nucleotide". It is suggested that all the claims be amended to clarify e.g. replace "which is capable of ligating" with "for ligation".

j. Claims 11-12 and 23-24 are each indefinite in the recitation "the mixture further comprises a set of probes containing all possible oligonucleotides of the common length 1" because it is unclear whether the "1" is the number of nucleotides in the oligonucleotide probe and the oligonucleotide probes have a length of 1 nucleotide. The recitation is further indefinite because it is unclear how an oligonucleotide, which inherently consists of more than one nucleotide, have a common length 1. It is suggested that the claims be amended to clarify.

k. Claim 13 is indefinite in the recitation "each primer is relatable to the variable sequence which variable sequences is relatable to the particular template" because "relatable" is a non-specific relational term and therefore the relationships between the primer and the variable sequence and between the variable sequence and the template is undefined. The recitation is further indefinite because "particular" is a non-specific relational term and therefore the relationship between the variable sequence and template are undefined. It is suggested that the claim be amended to define the relationships e.g. replace "is relatable to" with "identifies" and delete "particular".

l. Claims 21-22 are indefinite in steps (e) and (h) for the recitations "corresponding mass label" and "corresponding nucleotide sequence" because "corresponding" is a non-specific relational term and therefore the relationship between the "probe" and the "mass label" and

between the "mass label" and the "nucleotide sequence" are undefined. It is suggested that the claims be amended to define the relationships e.g. delete "corresponding".

m. Claims 21, 22, 23 and 24 are each indefinite because the claims are drawn to methods for characterizing DNA, but the methods do not recite steps for DNA characterization. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6. It is suggested that Claim 1 be amended to recite method steps of DNA characterization.

n. Claim 25 is indefinite in the recitation "relatable to its corresponding" because "relatable" and "corresponding" are both non-specific relational terms and therefore the relationship between the label and nucleotide is undefined. It is suggested that the claim be amended to clarify e.g. replace "relatable to its corresponding" with "identifies the".

o. Claim 26 is indefinite in the recitation "relatable to" because "relatable" is a non-specific relational term and therefore the relationship between the label and base sequence is undefined. It is suggested that the claim be amended to clarify e.g. replace "relatable to" with "identifies the".

p. Claim 25 and 26 provides for the use of a probe or probe set (Claim 25) and use of a set of oligonucleotide primers (Claims 26), but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 25 and 26 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102/103

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Southern et al. (WO95/04160, published 9 February 1995). As stated above, the claims are replete with relative, non-specific, redundant and

undefined terms and phrases. For purposes of examination, the examiner has interpreted the claims as noted below.

Regarding Claim 1, Southern et al. teach a method for characterizing DNA comprising: providing a population of DNA fragments, each having cleavably attached thereto a mass label for identifying a feature of that fragment; separating the fragments on the basis of their length i.e. by immobilization at spaced locations; cleaving each fragment in a mass spectrometer to release its mass label; and determining each mass label by mass spectroscopy to identify the fragment (page 20, line 7-page 21, line 23) wherein the length of the fragment is "read" by repeating the above steps (page 21, lines 16-23). The preceding rejection is based on judicial precedent following In re Fitzgerald, 205 USPQ 594 because Southern et al. is silent with regard to relating the feature of each fragment to the length of the fragment. However, relating the feature to the length of the fragment recited in Claims 1-26 is deemed to be inherent in the detecting the mass labels (i.e. feature) in Southern et al. because the labels of Southern et al. identify each feature (i.e. labeled probe) of the fragment and number of features of the fragment wherein each feature has a known length (page 2, lines 26-33) and therefore, detecting the labels, detects the number of features of known length and hence identifies the length of the fragment. The burden is on applicant to show that the claimed relating the feature to the length of the fragment is either different or non-obvious over that of Southern et al. Alternatively, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the detection of mass labels in the method of Southern et al. wherein unique labels are attached to features (i.e. probes) of known length and wherein multiple labeled features (i.e. probes) are ligated to form a fragment and to detect the labels and number of labels to relate the features to the length of the fragment.

Claim Rejections - 35 USC § 103

9. Claims 2-18 and 20-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Southern et al. (WO95/04160, published 9 February 1995) in view of Ness et al. (U.S. Patent No. 6,027,890, filed 22 July 1997) and Alberts (Molecular Biology of the Cell, 1994, page 298). As stated above, the claims are replete with relative, non-specific, redundant and undefined terms and phrases. For purposes of examination, the examiner has interpreted the claims as noted below.

Regarding Claim 2, Southern et al. teach the method further comprises providing at least one DNA single-stranded temple with a primer and generating the population of DNA fragments from the template wherein the population comprises at least one series of fragments wherein the feature of each fragment determined by each mass label relates to a nucleotide at one end of each fragment so that each nucleotide is related to a position in the template associated with the label so as to deduce the sequence of the template (Fig. 5) but they do not teach the series of fragments contains all possible lengths of a second strand of DNA complementary to the template. However, Ness et al. teach a similar method comprising: providing a population of DNA fragments, separating the fragments based on their length, cleaving each fragment; and determining the mass label to identify the fragment (Column 2, lines 55-67) wherein the fragments contains all possible length of a second strand DNA complementary to the template i.e. primer extension and incorporation of dideoxynucleotides (Column 53, lines 34-57) and it was known in the art at the time the claimed invention was made that primer extension dideoxynucleotide incorporation provided a series of fragments that contains all possible lengths of the template as taught by Alberts et al. (page 298). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the population of DNA fragments of Southern et al. and to provide fragments having all possible lengths as taught by Ness et al. for the obvious benefit of

characterizing DNA of interest completely by characterizing complementary fragments of all possible lengths.

Regarding Claim 3, Southern et al. teach the method wherein the series of DNA fragments is provided by contacting the template in the presence of DNA enzyme with a mixture of nucleotides sufficient for hybridizing to the template for forming a second strand of DNA complementary to the template and wherein the mixture further comprises a set of probes containing all four nucleotides wherein the probes comprise modified nucleotides and wherein the probes have a mass label cleavably attached and are blocked to prevent further polymerization (page 3, lines 24-32 and page 20, line 32-page 21, line 3) but they do not teach the DNA enzyme is a DNA polymerase. However, Ness et al. teach the similar method wherein the series of DNA fragments are provided by contacting the in the presence of ligating or polymerizing enzymes (i.e. DNA polymerase, Column 3, lines 21-29). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA enzyme of Southern et al. with the DNA polymerase of Ness et al. for the expected benefit of incorporating dideoxynucleotides to provide fragments having all possible lengths thereby to characterizing DNA of interest completely by characterizing complementary fragments of all possible lengths.

Regarding Claim 4, Southern et al. teach the method wherein the template is a plurality of template and the DNA fragments is provided by contacting each template in a separate reaction zone (i.e. spaced location) in the presence of a DNA enzyme with a mixture of nucleotides sufficient for hybridizing to the template to form a second strand of DNA complementary to the template and wherein the mixture further comprises a set of four probes containing all four nucleotides wherein the nucleotide of each probe comprises modified nucleotide which hybridizes to the second strand of DNA but is blocked to prevent further polymerization and has a mass label cleavably attached (page 3, lines 24-32, page 7, lines 26-34 and page 20, line 32-page 21, line 3) wherein the mass labels differ from other sets of labels

(page 2, lie 33-page 3, line 9) and wherein the fragments are pooled before step (ii) i.e. before immobilization on (page 20, lines 11-16) but they do not teach the DNA enzyme is a DNA polymerase. However, Ness et al. teach the similar method wherein the DNA enzyme is a DNA polymerase (Column 3, lines 21-29).

Regarding Claim 5, Southern et al. teach the method wherein the template is a plurality of template and the DNA fragments are provided by contacting each template in a separate reaction zone (i.e. spaced location) in the presence of a DNA enzyme with a mixture of nucleotides sufficient for hybridizing to the template to form a second strand of DNA complementary to the template wherein the mixture further comprises probes comprising modified nucleotides which hybridizes to the second strand of DNA but is blocked to prevent further polymerization and has a mass label cleavably attached (page 3, lines 24-32, page 7, lines 26-34 and page 20, line 32-page 21, line 3) wherein the mass labels differ from other sets of labels (page 2, lie 33-page 3, line 9) and wherein the fragments are pooled before step (ii) i.e. before immobilization on (page 20, lines 11-16) wherein the probe contains only one of the four nucleotides (Example 16b, page 44, lines 12-16) but they do not teach the DNA enzyme is a DNA polymerase. However, Ness et al. teach the similar method wherein the DNA enzyme is a DNA polymerase (Column 3, lines 21-29).

Regarding Claim 6, Southern et al. teach the method wherein the template is a plurality of templates and the DNA fragments are provided by contacting the templates in a separate reaction zones (i.e. spaced location) in the presence of a DNA enzyme with a mixture of nucleotides sufficient for hybridizing to the template for forming a second strand of DNA complementary to the template and wherein the mixture further comprises probes comprising modified nucleotides wherein the nucleotide of each probe comprises modified nucleotide which hybridizes to the second strand of DNA but is blocked to prevent further polymerization and has a mass label cleavably attached (page 3, lines 24-32, page 7, lines 26-34 and page 20, line 32-page 21, line 3) wherein the mass labels differ from other sets of labels (page 2, lie 33-page

3, line 9) wherein the probe contains only one of the four nucleotides (Example 16b, page 44, lines 12-16) but do not teach the DNA enzyme is a DNA polymerase._However, Ness et al. teach the similar method wherein the DNA enzyme is a DNA polymerase (Column 3, lines 21-29).

Regarding Claim 7, Southern et al. teach the method wherein the template is four sets of single-stranded DNA templates (page 5, lines 27-35) wherein the DNA fragments are provided by contacting each template in a separate reaction zone (i.e. spaced location) in the presence of a DNA enzyme with a mixture of nucleotides sufficient for hybridizing to the template for forming a second strand of DNA complementary to the template and wherein the mixture further comprises probes comprising modified nucleotides which hybridize to the second strand of DNA but are blocked to prevent further polymerization, wherein each fragment is terminated with the probe and wherein each of the templates is primed with a primer (i.e. linker) to which the mass label is cleavably attached (by ligation of the probe comprising the mass label to the linker) (page 3, lines 24-32, page 7, lines 26-34 and page 20, line 32-page 21, line 3) wherein the mass labels differ from other sets of labels (page 2, lie 33-page 3, line 9) and wherein the fragments are pooled before step (ii) i.e. before immobilization on (page 20, lines 11-16) wherein the probe contains only one of the four nucleotides i.e. wherein the probe is chosen to identify a specific position of the analyte chain (page 2, lines 2-8 and 26-32) but they do not teach the DNA enzyme is a DNA polymerase. However, Ness et al. teach the similar method wherein the DNA enzyme is a DNA polymerase (Column 3, lines 21-29).

Regarding Claim 8, Southern et al. teach the method wherein the template is a plurality of template and the DNA fragments is provided by contacting each template in a separate reaction zone (i.e. spaced location) in the presence of a DNA enzyme with a mixture of nucleotides sufficient for hybridizing to the template for forming a second strand of DNA complementary to the template and wherein the mixture further comprises a set of four probes containing all four nucleotides wherein the nucleotide of each probe comprises modified

nucleotide which hybridizes to the second strand of DNA but is blocked to prevent further polymerization and has a mass label cleavably attached (page 3, lines 24-32, page 7, lines 26-34 and page 20, line 32-page 21, line 3) wherein the mass labels are uniquely resolvable in a mass spectrometer (page 2, line 33-page 3, line 9) and wherein the fragments are pooled before step (ii) (i.e. before immobilization, page 20, lines 11-16) and sorted according to sub-sequence (i.e. according to vector sequence, page 17, lines 8-11) wherein the fragments are immobilized in sets (i.e. groups) to facilitate detection and simplify identification (page 18, lines 10-17) and wherein the fragments have a common sub-sequence length of 3-5 bases (i.e. the reporter groups adjacent to the linker (i.e. primer) comprise 2-20 residues, page 2, lines 26-33) but they do not teach the DNA enzyme is a DNA polymerase. However, Ness et al. teach the similar method wherein the DNA enzyme is a DNA polymerase (Column 3, lines 21-29).

Regarding Claim 9, Southern et al. teach the method wherein the series of DNA fragment is provided by contacting the template in the presence of a DNA enzyme with a mixture of nucleotides sufficient for hybridizing to the template to form a second strand of DNA complementary to the template, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridizing to the templates in which a nucleotide of each probe comprises a modified nucleotide which is capable of polymerizing (hybridizing) to the second strand of DNA but reversibly blocked (i.e. removable) to prevent further polymerization wherein the step of contacting forms a series of templates, each second strand terminated with one of the probes; removing unpolymerized nucleotide; unblocking the modified nucleotides; and contacting the templates with an array of probes wherein each probe has a nucleotide sequence of common length of 2 to 6 (page 2, lines 27-33 and Fig. 5) wherein each probe is cleavably attached to a mass label which is uniquely resolvable in mass spectrometry for identifying the nucleotide sequence (page 20, lines 7-36) but they do not teach the DNA enzyme is a DNA polymerase and they do not teach that contacting the template forms all possible lengths of second strand DNA. However, Ness et al. teach the similar method wherein the DNA

enzyme is a DNA polymerase (Column 3, lines 21-29) and wherein the fragments contains all possible length of a second strand DNA complementary to the template i.e. primer extension and incorporation of dideoxynucleotides (Column 53, lines 34-57) and it was known in the art at the time the claimed invention was made that primer extension dideoxynucleotide incorporation provided a series of fragments that contains all possible lengths of the template as taught by Alberts et al. (page 298).

Regarding Claim 10, Southern et al. teach the method wherein the template is a plurality of primer DNA single-stranded templates, each at a unique concentration (i.e. the templates are immobilized either singly or in small sets i.e. at a known or unique concentration) wherein the series of DNA fragment is provided by contacting the templates in the presence of a DNA enzyme with a mixture of nucleotides sufficient for hybridizing to the template to form a second strand of DNA complementary to the templates, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridizing to the templates in which a nucleotide of each probe comprises a modified nucleotide which is capable of (hybridizing) to the second strand of DNA but reversibly blocked (i.e. removable) to prevent further polymerization wherein the step of contacting forms a series of templates, each second strand terminated with one of the probes; removing unpolymerized nucleotide; unblocking the modified nucleotides; and contacting the templates with an array of probes wherein each probe has a nucleotide sequence of common length of 2 to 6 (page 2, lines 27-33) wherein each probe is cleavably attached to a mass label which is uniquely resolvable in mass spectrometry for identifying the nucleotide sequence (page 20, lines 7-36) but they do not teach the DNA enzyme is a DNA polymerase and they do not teach that contacting the template forms all possible lengths of second strand DNA. However, Ness et al. teach the similar method wherein the DNA enzyme is a DNA polymerase (Column 3, lines 21-29) and wherein the fragments contains all possible length of a second strand DNA complementary to the template i.e. primer extension and incorporation of dideoxynucleotides (Column 53, lines 34-57) and it

was known in the art at the time the claimed invention was made that primer extension dideoxynucleotide incorporation provided a series of fragments that contains all possible lengths of the template as taught by Alberts et al. (page 298).

Regarding Claim 11, Southern et al. teach the method wherein the series of DNA fragments is provided by contacting the template in the presence of DNA ligase with a mixture of oligonucleotides sufficient for hybridizing to the template for forming a second strand of DNA complementary to the template, the oligonucleotides each having a common length in the range of 2 to 6 (page 2, lines 27-33) wherein the mixture further comprise a set of probes containing all possible oligonucleotides of common length for hybridizing to the templates in which the oligonucleotide of each probe comprises a modified oligonucleotide which is capable of ligating to the second strand of DNA but blocked to prevent further ligation thereto and which is cleavably attached to a uniquely resolvable mass label for identifying the oligonucleotide and wherein each fragment is terminated with one of the probes (page 3, line 32-page 4, line 6, page 20, lines 7-36 and Fig 5) but they do not teach the series of DNA fragments comprises all possible lengths of second strand DNA and they do not teach oligonucleotides of a common length 1. However, Ness et al. teach the similar method wherein the oligonucleotide of the common length 1 (i.e. dideoxynucleotides) and wherein the fragments contains all possible length of a second strand DNA complementary to the template i.e. primer extension and incorporation of dideoxynucleotides (Column 53, lines 34-57) and it was known in the art at the time the claimed invention was made that primer extension dideoxynucleotide incorporation provided a series of fragments that contains all possible lengths of the template as taught by Alberts et al. (page 298).

Regarding Claim 12, Southern et al. teach the method wherein the template is a plurality of primer DNA single-stranded templates, each at a unique concentration (i.e. the templates are immobilized either singly or in small sets i.e. at a known or unique concentration) wherein the series of DNA fragment is provided by contacting the template in

the presence of a DNA ligase with a mixture of oligonucleotides sufficient for hybridizing to the templates to form a second strand of DNA complementary to the templates, the oligonucleotides each having a common length of 2 to 6 (page 2, lines 27-33) wherein the mixture further comprises a set of probe containing all possible oligonucleotides of the common length wherein the oligonucleotide of each probe comprises a modified oligonucleotide which is capable of ligating to the second strand of DNA but blocked to prevent further ligation thereto and which is cleavably attached to a uniquely resolvable mass label for identifying the modified oligonucleotide and wherein each fragment is terminated with one of the probes (page 3, line 32-page 4, line 6, page 20, lines 7-36 and Fig 5) but they do not teach the series of DNA fragments comprises all possible lengths of second strand DNA and they do not teach oligonucleotides of a common length 1. However, Ness et al. teach the similar method wherein the oligonucleotide of the common length 1 (i.e. dideoxynucleotides) and wherein the fragments contains all possible length of a second strand DNA complementary to the template i.e. primer extension and incorporation of dideoxynucleotides (Column 53, lines 34-57) and it was known in the art at the time the claimed invention was made that primer extension dideoxynucleotide incorporation provided a series of fragments that contains all possible lengths of the template as taught by Alberts et al. (page 298).

Regarding Claim 13, Southern et al. teach the method wherein the plurality of single-stranded templates is primed by hybridizing to a known sub-sequence common to each of the templates and array of primers each comprising a base sequence containing a common sequence complementary to the known sub-sequence (i.e. primer (linker) is a vector sequence which is common to all the clones, page 15, lines 23-28) and a variable sequence of common length in the range of 2 to 6 (page 2, lines 27-33 and Fig. 5) in which the array contains all possible sequences of that common length and the mass label cleavable attached to each primer is relatable to the variable sequences which is relatable to the template to be sequenced (page 16, lines 6-10).

Regarding Claim 14, Southern et al. teach the method wherein the step of sorting the pooled fragments comprises contacting the fragments with an array of spatially separate oligonucleotides each comprising a base sequence containing a common sequence complementary to the primer sequence and a variable sequence (i.e. a vector sequence plus the clone, page 15, lines 23-28) of the common length which array contains all possible variable sequences of the common length (page 15, lines 20-36).

Regarding Claim 15, Southern et al. teach the reaction zones are spaced locations on a support (page 20, lines 11-12) but they do not teach the locations are separate containers. Ness et al. teach the similar method wherein the reaction is PCR (Column 3, lines 21-28), but they are silent with regard to the reaction zone of the PCR reaction. However, PCR reactions separate containers wherein the container are the "reaction zone" was known and routinely practiced in the art at the time the claimed invention was made. It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the reaction zone of Southern et al. with the routinely practiced PCR separate container reaction zone in the PCR reaction of Ness et al. for the obvious benefit of isolating the reactions to prevent cross-contamination between the reactions.

Regarding Claim 16, Southern et al. teach the method wherein the mixture of nucleotides comprises ATP, GTP, TTP, and CTP (Fig. 5).

Regarding Claim 17, Southern et al. teach the modified nucleotides are deoxynucleotides (DNA) (Fig. 5).

Regarding Claim 18, Southern et al. teach the method wherein the primed DNA is immobilized on a solid support (page 20, lines 11-20).

Regarding Claim 20, Southern et al. teach the method wherein each mass label is cleavably attached to a fragment by a linker cleavable in a mass spectrometer (page 9, lines 29-34).

Regarding Claim 21, Southern et al. teach a method for characterizing DNA comprising: providing a primed DNA single-stranded template; contacting the template in the presence of a DNA enzyme with a mixture of nucleotides sufficient for hybridizing to the template for forming a second strand of DNA complementary to the template, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridizing to the templates in which a nucleotide of each probe comprises a modified nucleotide which is capable of polymerizing (hybridizing) to the second strand of DNA but reversibly blocked to prevent further polymerization thereto, wherein the step of contacting forms a series of templates, each terminated with one of the probes; removing unpolymerized nucleotides; unblocking the modified nucleotides; contacting the templates with an array of oligonucleotide probes to form a series of fragments, each probe having a sequence of common length of 2 to 6 (page 2, lin2 27-33) wherein each probe is cleavably attached to a uniquely resolvable mass label for identifying the nucleotide sequence; separating the fragments from one another; cleaving each fragment to release the mass label; and determining each mass label by mass spectrometry to relate its sequence to a position in the template so as to deduce the sequence of the template (page 15, line 20-page 16, line 25) but they do not teach the DNA enzyme is a DNA polymerase. However, Ness et al. teach the similar method wherein the series of DNA fragments are provided by contacting the in the presence of ligating or polymerizing enzymes (i.e. DNA polymerase, Column 3, lines 21-29). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA enzyme of Southern et al. with the DNA polymerase of Ness et al. for the expected benefit of incorporating dideoxynucleotides to provide fragments having all possible lengths thereby to characterizing DNA of interest completely by characterizing complementary fragments of all possible lengths.

Regarding Claim 22, Southern et al. teach a method for characterizing DNA comprising: providing a plurality of primed DNA single-stranded templates, each at a unique concentration (i.e. the templates are immobilized either singly or in small sets i.e. at a known or unique

concentration); contacting the template in the presence of a DNA enzyme with a mixture of nucleotides sufficient for hybridizing to the template for forming a second strand of DNA complementary to the template, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridizing to the templates in which a nucleotide of each probe comprises a modified nucleotide which is capable of polymerizing (hybridizing) to the second strand of DNA but reversibly blocked to prevent further polymerization thereto, wherein the step of contacting forms a series of templates, each terminated with one of the probes; removing unpolymerized nucleotides; unblocking the modified nucleotides; contacting the templates with an array of oligonucleotide probes to form a series of fragments, each probe having a sequence of common length 2 to 6 (page 2, lines 27-33) wherein each probe is cleavably attached to a uniquely resolvable mass label for identifying the nucleotide sequence; separating the fragments from one another; cleaving each fragment to release the mass label; and determining each mass label by mass spectrometry to relate its sequence to a position in the template so as to deduce the sequence of the template (page 15, line 20-page 16, line 25) but they do not teach the DNA enzyme is a DNA polymerase. However, Ness et al. teach the similar method wherein the series of DNA fragments are provided by contacting the in the presence of ligating or polymerizing enzymes (i.e. DNA polymerase, Column 3, lines 21-29). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA enzyme of Southern et al. with the DNA polymerase of Ness et al. for the expected benefit of incorporating dideoxynucleotides to provide fragments having all possible lengths thereby to characterizing DNA of interest completely by characterizing complementary fragments of all possible lengths.

Regarding Claim 23, Southern et al. teach a method for characterizing DNA comprising: providing a primed DNA single-stranded template; contacting the template in the presence of DNA ligase with a mixture of oligonucleotides sufficient for hybridizing to the template for forming a second strand of DNA complementary to the template, the oligonucleotides each

having a common length in the range 2 to 6 (page 2, lines 27-33 and Fig. 5), wherein the mixture further comprise a set of probes containing all possible oligonucleotides of common length for hybridizing to the templates in which the oligonucleotide of each probe comprises a modified oligonucleotide which is capable of ligating to the second strand of DNA but blocked to prevent further ligation thereto and which is cleavably attached to a uniquely resolvable mass label for identifying the oligonucleotide and wherein each fragment is terminated with one of the probes; separating the fragments by immobilization; cleaving each fragment to release its mass label; and determining each mass label by mass spectrometry to relate it corresponding oligonucleotide to a position in the template so as to deduce the sequence of the template. (page 15, line 20-page 16, line 25) but they do not teach the series of DNA fragments comprises all possible lengths of second strand DNA and they do not teach oligonucleotides of a common length 1. However, Ness et al. teach the similar method wherein the oligonucleotide of the common length 1 (i.e. dideoxynucleotides) and wherein the fragments contains all possible length of a second strand DNA complementary to the template i.e. primer extension and incorporation of dideoxynucleotides (Column 53, lines 34-57) and it was known in the art at the time the claimed invention was made that primer extension dideoxynucleotide incorporation provided a series of fragments that contains all possible lengths of the template as taught by Alberts et al. (page 298).

Regarding Claim 24, Southern et al. teach a method for characterizing DNA comprising: providing a primed DNA single-stranded template each at a unique concentration (i.e. the templates are immobilized either singly or in small sets i.e. at a known or unique concentration); contacting the template in the presence of DNA ligase with a mixture of oligonucleotides sufficient for hybridizing to the template for forming a second strand of DNA complementary to the template, the oligonucleotides each having a common length in the range 2 to 6 (page 2, lines 27-33 and Fig. 5), wherein the mixture further comprise a set of probes containing all possible oligonucleotides of common length for hybridizing to the templates in

which the oligonucleotide of each probe comprises a modified oligonucleotide which is capable of ligating to the second strand of DNA but blocked to prevent further ligation thereto and which is cleavably attached to a uniquely resolvable mass label for identifying the oligonucleotide and wherein each fragment is terminated with one of the probes; separating the fragments by immobilization; cleaving each fragment to release its mass label; and determining each mass label by mass spectrometry to relate it corresponding oligonucleotide to a position in the template so as to deduce the sequence of the template. (page 15, line 20-page 16, line 25) but they do not teach the series of DNA fragments comprises all possible lengths of second strand DNA and they do not teach oligonucleotides of a common length 1. However, Ness et al. teach the similar method wherein the oligonucleotide of the common length 1 (i.e. dideoxynucleotides) and wherein the fragments contains all possible length of a second strand DNA complementary to the template i.e. primer extension and incorporation of dideoxynucleotides (Column 53, lines 34-57) and it was known in the art at the time the claimed invention was made that primer extension dideoxynucleotide incorporation provided a series of fragments that contains all possible lengths of the template as taught by Alberts et al. (page 298).

Regarding Claim 25, Southern et al. teach probes comprising a modified nucleotide which is capable of polymerizing (hybridizing) to a second strand of DNA complementary to the template but blocked to prevent further polymerization thereto, wherein the modified nucleotide is cleavably attached to a mass label for identifying the modified nucleotide and wherein the mass label is cleavable from the probe in a mass spectrometer and is resolvable by mass spectrometry and is relatable to its corresponding modified nucleotide (page 15, line 29-page 16, line 10).

Regarding Claim 26, Southern et al. teach oligonucleotide primers (i.e. linkers) each primer comprising a mass label cleavably attached to an oligonucleotide primer base sequence wherein each mass label is cleavable from the primer in a mass spectrometer and is uniquely

resolvable in relation to every other mass label and is relatable to the oligonucleotide primer base sequence (page 9, lines 5-34).

10. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Southern et al. (WO95/04160, published 9 February 1995) in view of Smith, L. M. (Nature, 1991, 349: 812-813). As stated above, the claims are replete with relative, non-specific, redundant and undefined terms and phrases. For purposes of examination, the examiner has interpreted the claims as noted below.

11. Regarding Claim 19, Southern et al. teach a method for characterizing DNA comprising: providing a population of DNA fragments, each having cleavably attached thereto a mass label for identifying a feature of that fragment; separating the fragments on the basis of their length i.e. by immobilization at spaced locations; cleaving each fragment in a mass spectrometer to release its mass label; and determining each mass label by mass spectroscopy to identify the fragment (page 20, line 7-page 21, line 23) wherein the length of the fragment is "read" by repeating the above steps (page 21, lines 16-23) but they do not teach the method of separating the fragments is effected by capillary electrophoresis. However, capillary electrophoresis was well know in the art at the time the claimed invention was made as taught by Smith who teaches capillary electrophoresis provides for rapid analysis of long DNA sequences (page 812, left column, second paragraph). It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the separation of Southern et al. with the capillary electrophoresis taught by Smith for the expected benefits taught by the latter i.e. rapid analysis of long DNA sequences (page 812, left column, second paragraph).

Prior Art

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Dubiley et al. (Nucleic Acids Research, 1997, 25(12): 2259-2265) teach a method for characterizing DNA comprising providing a population of DNA fragments and contacting with a mixture comprising probes having mass labels.

Conclusion

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BJ Forman whose telephone number is (703) 306-5878. The examiner can normally be reached on 6:45 TO 4:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-8724 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BJ Forman, Ph.D.
June 13, 2001

JEFFREY FREDMAN
PRIMARY EXAMINER